PB89-120273

Health and Environmental Effects Profile for Niagara Blue 48

(U.S.) Environmental Protection Agency
Cincinnati, OH

May 87

U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA/600/X-87-389	2.
3. RECIPIENT'S ACCESSION NO. PB89 120273/AS	
4. TITLE AND SUBTITLE: Health and Environmental Effects Profile for Niagara Blue 4B	5. REPORT DATE: May 1987
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS: Environmental Criteria and Assessment Office, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE: EPA/600/22
15. SUPPLEMENTARY NOTES	

16. ABSTRACT

The Health and Environmental Effects Profile for Niagara Blue 4B was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine a Reference Dose (RfD) or a carcinogenic potency factor for Niagara Blue 4B.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group

18. DISTRIBUTION STATEMENT: Public	19. SECURITY CLASS (This Report): Unclassified	21. NO. OF PAGES: 51
	20. SECURITY CLASS (This page): Unclassified	22. PRICE: DF 15.95 / MF A03/LP5

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB89-120273

EPA/600/X-87/389
May 1987

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR NIAGARA BLUE 4B

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL INFORMATION SERVICE
SPRINGFIELD, VA. 22161

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

EXECUTIVE SUMMARY

Niagara Blue 4B is a common name for the commercial azo dye Direct Blue 15, which is produced by the coupling of o-dianisidine with 1-amino-8-naphthol-3,6-disulfonic acid under alkaline conditions. It is soluble in water, but is insoluble in most organic solvents (Society of Dyers and Colourists, 1971a). It can be used to dye or stain cellulose, leather, paper, cotton, silk, wool and biological materials, and tint cinematograph films (Society of Dyers and Colourists, 1971b). Four U.S. manufacturers produced 0.270 million pounds of Niagara Blue 4B in 1982 (USITC, 1983). Five U.S. companies currently market the dye under various tradenames (AATCC, 1985). Importation of this dye through principal U.S. customs districts was 8810 pounds in 1983 (USITC, 1984).

Experimental environmental fate data specific to Niagara Blue 4B are very limited. Brown and Laboureur (1983) found that Niagara Blue 4B can be substantially biodegraded under anaerobic conditions. If released to water, Niagara Blue 4B may be susceptible to significant adsorption because dyestuffs by their substantive nature (ability to be exhaustively deposited from aqueous baths to fibers) are likely to be adsorbed onto both silts and sediment of rivers and lakes (Brown and Laboureur, 1983). Removal of adsorbed Niagara Blue 4B may occur by anaerobic biodegradation. In general, direct dyes are expected to be relatively stable to direct photolysis in natural waters (Porter, 1973). But humic materials in natural water have been found to strongly accelerate the indirect photodecomposition of azo dyes (Haag and Mill, 1985). Hydrolysis, volatilization and bioconcentration are not expected to be significant. Apparently, indirect photolysis,

microbial degradation and adsorption are the important fate processes in water. In the atmosphere, Niagara Blue 4B will probably be present as particulate matter and dusts and may be removed from the atmosphere by wet and dry deposition. In soil, Niagara Blue 4B may not leach significantly since dyestuffs are susceptible to significant adsorption. It is susceptible to anaerobic biodegradation in soils (Brown and Laboureur, 1983). Photodegradation in soil may not be significant beyond the surface layer. The role of chemical oxidation/reduction in soils remains unknown.

Occupational exposure to Niagara Blue 4B occurs during its production and its use in dyeing. Wastewater effluents are probably the major source of release to the environment. Ambient monitoring data could not be located in the available literature.

Pertinent data regarding the effects of Niagara Blue 4B on aquatic biota could not be located in the available literature as cited in the Appendix.

As indicated by excretion studies, at least 18% of an oral dose of Niagara Blue 4B was absorbed from the gastrointestinal tract of rats and was widely distributed throughout the body (Bowman et al., 1982). 3,3'-Dimethoxybenzidine has been identified in the urine of workers occupationally exposed to the dyes (Lowry et al., 1980; Genin, 1977) and in the urine of rats and dogs treated orally with Niagara Blue 4B (Bowman et al., 1982; Lynn et al., 1980). Alkaline hydrolyzable conjugates monoacetyl 3,3'-dimethoxybenzidine and diacetyl-3,3'-dimethoxybenzidine were also found in the urine of the rats (Bowman et al., 1982; Lynn et al., 1980). Peak excretion of radioactivity occurred 8-16 hours after oral exposure to Niagara Blue 4B in rats (Bowman et al., 1982). Approximately 75 and 19% was excreted in the feces and urine, respectively.

Specific Niagara Blue 4B bioassay data could not be located in the available literature as cited in the Appendix. It is clear, however, that Niagara Blue is metabolized in part to 3,3-dimethoxybenzidine which has been implicated as a carcinogen in animal test systems and exposed humans. IARC considers 3,3-dimethoxybenzidine to have sufficient evidence for animal carcinogenicity, Group 2B. Based upon the evidence reviewed by IARC and preliminary results of an NTP bioassay which suggest positive results, 3,3-dimethoxybenzidine would be placed in EPA Group B2. In view of the data indicating that 3,3-dimethoxybenzidine is a metabolate of Niagara Blue 4B, Niagara Blue should also be considered to fall in EPA weight of the evidence category B2.

The mutagenicity of Niagara Blue 4B in frameshift sensitive tester strains of Salmonella typhimurium was greatly enhanced when flavin mononucleotide (a reducing agent) or gut flora reduction was included in the testing (Reid et al., 1984; Prival et al., 1982, 1984). This finding indicates that reduction of the azo bond is one important step in activating Niagara Blue 4B to a mutagen. In an abstract, no increases in unscheduled DNA systhesis were reported in rat hepatocytes after in vivo or in vitro exposures to Niagara Blue 4B (Mirsalis et al., 1983). In another abstract increased mutant colonies were reported in L51784 mouse lymphoma cells with S9 metabolic activation (Rudd et al., 1983).

No data regarding teratogenic effects after oral or inhalation exposure to Niagara Blue 4B were available. Niagara Blue 4B caused a dose-related increase in resorption and malformed fetuses in rats following intraperitoneal injection (Beaudoin, 1968) and increased resorptions in rats following subcutaneous injection (Lloyd and Beck, 1966). Pertinent data regarding the reproductive effects of Niagara Blue 4B could not be located in the available literature as cited in the Appendix.

The chronic and subchronic toxicity of Niagara Blue 4B has not been adequately described. The only study found was a 30-day study in which the only effects observed in rats dosed with 1000 mg/kg/day, 5 days/week were blue coloration, increased kidney weight and decreased adrenal weight (Leist, 1982). These effects were not observed in rats after a 2-week recovery period.

Data were insufficient to derive an RfD, RQ, q_1^* or F factor. Because Niagara Blue 4B is metabolized to 3,3'-dimethoxybenzidine, an EPA Group B2 chemical and IARC Group 2B, the dye is placed in EPA Group B2, probable human carcinogen.

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	4
1.5.	SUMMARY	4
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	5
2.1.	WATER	5
2.1.1.	Hydrolysis	5
2.1.2.	Oxidation/Reduction	5
2.1.3.	Photolysis	5
2.1.4.	Microbial Degradation	6
2.1.5.	Volatilization	6
2.1.6.	Adsorption	6
2.1.7.	Bioconcentration	7
2.2.	AIR	7
2.3.	SOIL	7
2.4.	SUMMARY	8
3.	EXPOSURE	10
3.1.	WATER	10
3.2.	FOOD	11
3.3.	INHALATION	11
3.4.	DERMAL	11
3.5.	SUMMARY	11
4.	PHARMACOKINETCS	12
4.1.	ABSORPTION	12
4.2.	DISTRIBUTION	12
4.3.	METABOLISM	13
4.4.	EXCRETION	14
4.5.	SUMMARY	14
5.	EFFECTS	16
5.1.	CARCINOGENICITY	16
5.1.1.	Animal Studies	16
5.1.2.	Human Studies	16

TABLE OF CONTENTS (cont.)

		Page
5.2.	MUTAGENICITY	16
5.3.	TERATOGENICITY	18
5.4.	OTHER REPRODUCTIVE EFFECTS	19
5.5.	CHRONIC AND SUBCHRONIC TOXICITY	19
5.6.	OTHER RELEVANT INFORMATION	20
5.7.	SUMMARY	20
6.	AQUATIC TOXICITY	22
7.	EXISTING GUIDELINES AND STANDARDS	23
7.1.	HUMAN	23
7.2.	AQUATIC	23
8.	RISK ASSESSMENT	24
9.	REPORTABLE QUANTITIES	27
9.1.	REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY	27
9.2.	WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY	27
10.	REFERENCES	30
APPENDIX:	LITERATURE SEARCHED	36

LIST OF ABBREVIATIONS

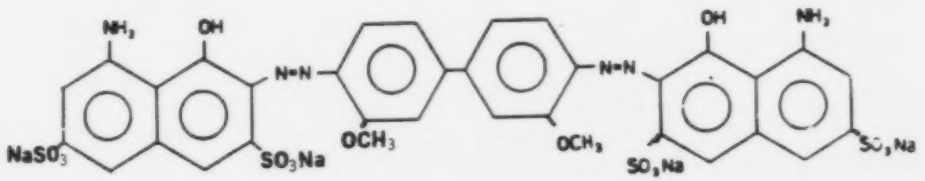
CAS	Chemical Abstract Service
FMN	Flavin mononucleotide
GC	Gas chromatography
K_{ow}	Octanol/water partition coefficient
LD_{50}	Dose lethal to 50% of recipients
MS	Mass spectrometry
RFD	Reference dose
RQ	Reportable Quantity
SD	Standard deviation
UDS	Unscheduled DNA synthesis

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Niagara Blue 4B is commonly referred to as Direct Blue 15; the Colour Index reference number is C.I. 24400 (Society of Dyers and Colourists, 1971a). The current CAS designation for Niagara Blue 4B is 2,7-naphthlene-disulfonic acid, 3,3'-[3,3'-dimethoxy[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis [5-amino-4-hydroxy-], tetrasodium salt. Direct Blue 15 is currently marketed in the United States under the following tradenames (AATCC, 1985): Amidine Sky Blue 5B Ex. (John Campbell & Co.), Atlantic Direct Sky Blue M Liq. (Atlantic Industries), Pergasol Sky Blue M Liq. (Ciba-Geigy Corp.), Phenamine Sky Blue A Liq. (BASF Wyandotte), Pontamine Sky Blue MW Liq. (Mobay Chem.).

The structure, molecular weight, empirical formula and CAS Registry number for Niagara Blue 4B are as follows:



Molecular weight: 996.9

Empirical formula: $C_{34}H_{28}N_6O_{16}S_4Na_4$

CAS Registry number: 2429-74-5

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Niagara Blue 4B is soluble in water, forming a reddish-blue solution, and insoluble in most organic solvents (Society of Dyers and Colourists, 1971a). All direct dyes are water soluble and form anions by dissociation

(Kuehni et al., 1979). In aqueous solution, the molecules of direct dyestuffs are linked by hydrogen bonds forming larger agglomerates or colloidal solutions, which reduces their solubility and promotes disposition on cellulosic fibers. The structure of these agglomerates allows firm linkage to the cellulose molecule by multiple hydrogen bonds (Kuehni et al., 1979).

Physical properties such as melting point, boiling point, vapor pressure, density and log K_{ow} could not be located in the available literature. Lack of appropriate fragment values precluded the computer calculation of log K_{ow} (U.S. EPA, 1986a). The air conversion factor for Niagara Blue 4B is 1 ppm = 41.44 mg/m³.

The manufacture and testing of Niagara Blue 4B probably do not conform to rigid chemical specifications, and its composition may vary in order to meet shade and intensity requirements.

1.3. PRODUCTION DATA

Niagara Blue 4B is produced by coupling o-dianisidine to 2 mol of H acid (1-amino-8-naphthol-3,6-disulfonic acid) under alkaline conditions (Society of Dyers and Colourists, 1971a).

In 1982, four U.S. manufacturers produced 0.270 million pounds of Niagara Blue 4B (USITC, 1983), the most recent production figure available. In 1984, Atlantic Industries, Sandoz Color & Chemical and Mobay Chemical were listed as manufacturers (USITC, 1985). Five U.S. companies currently market the dye under various tradenames (AATCC, 1985) (see Section 1.1.). The production data available from the public portion of the U.S. EPA TSCA Production File for 1977 are listed in Table 1-1.

Importation of Niagara Blue 4B through principal U.S. customs districts was 8810 pounds in 1983 (USITC, 1984) and 7716 pounds in 1980 (USITC, 1981).

TABLE 1-1

Niagara Blue 4B Production Data for 1977*

Producer/Location	Manufacturer/Importer	Production Range (pounds)
DuPont Puerto Rico Manati, PR	manufacturer	confidential
DuPont Deepwater, NJ	manufacturer	1-10 thousand
Mobay Chemical Bayonne, NJ	manufacturer	confidential
Atlantic Chemical Nutley, NJ	manufacturer	10-100 thousand
Toms River Chemical Toms River, NJ	manufacturer	confidential
Hilton-Davis Chemical Cincinnati, OH	manufacturer	none
GAF Corp. Rensselaer, NY	manufacturer	0.1-1 million
American Hoechst Bridgewater, NJ	importer	confidential

*Source: U.S. EPA, 1977

1.4. USE DATA

Niagara Blue 4B is a dye that can be used to dye cellulose, leather and paper; stain cotton, silk, wool and biological materials; and tint cinematographic film (Society of Dyers and Colourists, 1971b).

1.5. SUMMARY

Niagara Blue 4B is a common name for the commercial azo dye Direct Blue 15, which is produced by the diazotization of o-dianisidine with 1-amino-8-naphthol-3,6-disulfonic acid under alkaline conditions. It is soluble in water, but is insoluble in most organic solvents (Society of Dyers and Colourists, 1971a). It can be used to dye or stain cellulose, leather, paper, cotton, silk, wool and biological materials, and tint cinematographic films (Society of Dyers and Colourists, 1971b). Four U.S. manufacturers produced 0.270 million pounds of Niagara Blue 4B in 1982 (USITC, 1983). Five U.S. companies currently market the dye under various tradenames (AATCC, 1985). Importation of this dye through principal U.S. customs districts was 8810 pounds in 1983 (USITC, 1984).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Experimental hydrolysis data could not be located in the available literature as cited in the Appendix; however, since Niagara Blue 4B does not contain functional groups that are readily susceptible to environmental hydrolysis, hydrolysis is not expected to be environmentally significant.

2.1.2. Oxidation/Reduction. Specific experimental data regarding Niagara Blue 4B could not be located in the available literature. Takemura et al. (1965) reported that bubbling H_2S through a pure azo-dye solution yields aromatic amines, and suggested that azo dyes in wastewater may be reduced at the azo linkage (by H_2S or SO_2 in the water) to form intermediates such as benzidine or naphthylamine from which the dye is produced; however, a water system receiving dyes would have to be very polluted so that H_2S or SO_2 (or a reducing environment) would significantly convert the dye.

2.1.3. Photolysis. Porter (1973) examined the photodegradation rate in aqueous solution of 8 direct dyes and 12 other azo dyes in artificial light and 1 direct dye and 1 basic dye in natural sunlight. Based on the experimental results, the author concluded that direct dyes are relatively stable to direct photolysis in natural waters. Although Niagara Blue 4B was not studied, its structure is similar to several dyes that were tested.

Haag and Mill (1985) examined the aqueous photodegradation rate of 15 azo dyes by simulated and natural sunlight. Significant direct photolysis was observed for some dyes. In natural water, humic materials were found to strongly accelerate the photodecomposition rate of all the dyes. Therefore, indirect photolysis may be an important removal mechanism for azo dyes in water.

2.1.4. Microbial Degradation. Brown and Laboureur (1983) reported that a number of azo dyes, including Niagara Blue 4B, were substantially biodegraded under anaerobic test conditions. The average primary biodegradation (loss of color) of Niagara Blue 4B was 83% by anaerobic sludge inoculum obtained either from a digester of a sewage treatment works or from a laboratory digester operated under a specified protocol. Although the biodegradation study was continued for 42 days, it is not clear whether the reported degradation for Niagara Blue 4B was attained in 42 days. The authors suggested that the breakdown of dyestuffs in the environment may be initiated under anaerobic conditions.

Brown et al. (1981) measured the aerobic respiration rate of activated sludge in the presence of Niagara Blue 4B and concluded that the dye is unlikely to be significantly toxic to aerobic sewage treatment at concentrations normally reaching these facilities.

2.1.5. Volatilization. Experimental data could not be located in the available literature as cited in the Appendix; however, since Niagara Blue 4B is soluble in water (Society of Dyers and Colourists, 1971a) and is expected to have a relatively low vapor pressure based on its chemical structure, a relatively small Henry's Law constant is expected. Therefore, volatilization from water is not expected to be significant in the environment.

2.1.6. Adsorption. Experimental data specific to Niagara Blue 4B could not be located in the available literature as cited in the Appendix. Because of their substantive nature (ability to be exhaustively deposited from aqueous baths to fibers), dyestuffs are likely to be adsorbed onto both sewage works sludge and onto silts and sediments of rivers and lakes (Brown and Laboureur, 1983). In conventional biological waste treatment systems,

soluble dye removal usually occurs when the dye is adsorbed onto sludge (Porter, 1973). Sewage works sludge is usually treated by anaerobic digestion or landfilling; therefore, removal of the dye from the sludge may occur by anaerobic biodegradation. Similar anaerobic conditions exist in many lakes and rivers with respect to adsorbed material on silts and sediments and, therefore, adsorbed dyes may be subject to anaerobic degradation in the environment (Brown and Laboureur, 1983).

2.1.7. **Bioconcentration.** Experimental data could not be located in the available literature. Since Niagara Blue 4B is water soluble (Society of Dyers and Colourists, 1971a), bioconcentration in aquatic organisms is not expected to be significant.

2.2. AIR

Niagara Blue 4B in the atmosphere is most likely to be associated with particulate matter and dusts, especially from atmospheric effluents resulting from production and use. These particulate matter and dusts are subject to wet and dry deposition. Since the compound contains amine substituents, it may also undergo heterogeneous oxidation reactions with HO radical present in the atmosphere; however, none of the atmospheric fate processes of this compound have been studied.

2.3. SOIL

Pertinent experimental data could not be located in the available literature as cited in the Appendix. The role of chemical oxidation and reduction in soil is not clear, although it is known that dyes, in general, are resistant to oxidation by ozone, chlorine and oxides of nitrogen (Porter, 1973). Hydrolysis may not be significant since this compound does not contain hydrolyzable groups. Because of light attenuation and scattering, photolysis may not be significant beyond the surface layer of soil.

Brown and Laboureur (1983) have shown that Niagara Blue 4B and other azo dyes are susceptible to anaerobic biodegradation. The ability of Niagara Blue 4B to undergo aerobic biodegradation is not clear but appears to be unlikely (Porter, 1973).

Since Niagara Blue 4B is water soluble (Society of Dyers and Colourists, 1971a), leaching in soil might be expected; however, the substantive nature of dyestuffs (Brown and Laboureur, 1983), including the direct dyes (Kuehni et al., 1979), indicates that significant adsorption to soil may occur. Therefore, significant leaching in soil may not occur.

2.4. SUMMARY

Experimental environmental fate data specific to Niagara Blue 4B are very limited. Brown and Laboureur (1983) found that Niagara Blue 4B can be substantially biodegraded under anaerobic conditions. If released to water, Niagara Blue 4B may be susceptible to significant adsorption because dyestuffs by their substantive nature (ability to be exhaustively deposited from aqueous baths to fibers) are likely to be adsorbed onto both silts and sediment of rivers and lakes (Brown and Laboureur, 1983). Removal of adsorbed Niagara Blue 4B may occur by anaerobic biodegradation. In general, direct dyes are expected to be relatively stable to direct photolysis in natural waters (Porter, 1973). But humic materials in natural water have been found to strongly accelerate the indirect photodecomposition of azo dyes (Haag and Mill, 1985). Hydrolysis, volatilization and bioconcentration are not expected to be significant. Apparently, indirect photolysis, microbial degradation and adsorption are the important fate processes in water. If released to the atmosphere, Niagara Blue 4B will probably be present as particulate matter and dusts and may be removed from the atmosphere by wet and dry deposition. In soil, Niagara Blue 4B may not leach significantly since dyestuffs are susceptible to significant adsorption.

It is susceptible to anaerobic biodegradation in soils (Brown and Laboureur, 1983). Photodegradation in soil may not be significant beyond the surface layer. The role of chemical oxidation/reduction in soils remains unknown.

3. EXPOSURE

Niagara Blue 4B has not been reported to occur in nature; therefore, exposure from natural sources is not expected to occur. Occupational exposure to Niagara Blue 4B occurs during its production and use for the dyeing of various products. Likely routes of exposure are inhalation of particulates and dermal exposure. Based on a National Occupational Hazard Survey conducted between 1972 and 1974, it is estimated that 70 U.S. workers are potentially exposed to Niagara Blue 4B (NIOSH, 1984).

3.1. WATER

Pertinent monitoring data for Niagara Blue 4B in water could not be located in the available literature as cited in the Appendix. For the organic dye industry, in general, it has been estimated that ~90% of the dye ends up on the fabric, while 10% is lost to wastewater effluents during dyeing operations (Porter, 1973; Brown et al., 1981). Losses of dyes to wastewater effluents during manufacture have been estimated to be 1-2% (Brown et al., 1981). Waste streams from dye manufacture contain dissolved inorganic salts and small amounts of dye and dye intermediates (Steadman et al., 1977). Wastewater effluents are, therefore, the major source of release to the aquatic environment; the efficiency of wastewater treatment operations determines the amount of dye that reaches natural waters.

Release of dye from textile fabrics may occur from commercial or consumer washing; however, dyes in most finished products are considered to be essentially "fast" (they do not migrate or wash out) (Jones, 1979). Various after-treatments are commonly applied to fabrics dyed with direct dyes to improve their colorfastness (Kuehni et al., 1979).

3.2. FOOD

Pertinent data regarding exposure to Niagara Blue 4B through food could not be located in the available literature as cited in the Appendix.

3.3. INHALATION

Pertinent ambient or occupational air monitoring data specific to Niagara Blue 4B could not be located in the available literature as cited in the Appendix.

Ambient atmospheric emissions may occur from ventilation effluents at production and use sites. In addition, air effluents from production operations such as spray drying may be sources of release. Particulate emissions from these sources are usually filtered at plant sites, which should reduce significantly the amount of particulate matter actually reaching the ambient atmosphere.

3.4. DERMAL

Pertinent monitoring data regarding dermal exposure of Niagara Blue 4B could not be located in the available literature as cited in the Appendix. The general public is exposed primarily to finished dyes after they have been applied to products; however, there is little chance of dyes coming off in perspiration, saliva or washings if label instructions are followed (Jones, 1979).

3.5. SUMMARY

Occupational exposure to Niagara Blue 4B occurs during its production and its use in dyeing. Wastewater effluents are probably the major source of release to the environment. No ambient monitoring data were located in the available literature.

4. PHARMACOKINETICS

4.1. ABSORPTION

Bowman et al. (1982) found that male Fischer 344 rats excreted 18.8% of a dose of radioactivity in the urine collected for 192 hours after a single oral dose of 12 mg/kg of ^{14}C-Niagara Blue 4B. Approximately 13.1% of the dose was excreted in the first 24 hours and 17.6% of the dose was excreted in the first 48 hours. Fecal excretion over 192 hours accounted for 74.4% of the dose of radioactivity, with 61% of the dose excreted in the first 24 hours. Since biliary excretion was not measured, it is not known how much of the fecal excretion was due to excretion in the bile. These results indicate that ~18.8% of the dose was absorbed from the gastrointestinal tract. No data were located that evaluated absorption by the inhalation or dermal route.

4.2. DISTRIBUTION

Beaudoin and Pickering (1960) looked for Niagara Blue 4B in various tissues after intraperitoneal injection of a 140 mg/kg dose in a 2% aqueous solution was given to pregnant Sherman rats on day 8 of gestation. Rats were killed on gestation day 20 and tissues were examined. Dye granules were detected in the macrophages of the lungs, liver, uterus, ovary, spleen and lymph nodes. The dye was also found in the basal portion of the proximal tubules of the kidneys and in the placenta and in the yolk sac, which accumulated the most dye.

Bowman et al. (1982) administered 12 mg/kg ^{14}C-labeled Niagara Blue 4B in 1 ml distilled water to 18 male Fischer 344 rats by oral intubation. At 2, 4, 8, 12, 24 or 72 hours after dosing, three rats were killed and samples from tissues, organs, fluids, carcass, and urine and feces were collected for analysis by radiochemical assays. ^{14}C was widely distributed throughout the body. Other than the gastrointestinal tract, the highest

levels of ^{14}C were found in the liver, kidney, lung and carcass. The lung level of ^{14}C peaked at 4 hours, while ^{14}C content of other tissues peaked at 8 hours. Compared with other organs, the liver accumulated a significant amount of radioactivity, with 1.14 µg equivalents at 72 hours. Tissue levels for other nonexcretory organs were $\leq$0.06 µg equivalents at 72 hours.

4.3. METABOLISM

Lowry et al. (1980) observed dimethoxybenzidine in the urine of workers occupationally exposed to 3,3'-dimethoxybenzidine-based dyes. Similar results were reported by Genin (1977).

Bowman et al. (1982) gave 20 male Fischer 344 rats an oral dose of 12 mg/kg Niagara Blue 4B and, using GC and radiochemical assays, looked for the metabolites in urine collected at varying intervals until 192 hours after dosing. Four control rats received water. Excretion of ^{14}C peaked during the 8- to 16-hour interval; no metabolites were detected by GC after 25 hours. The metabolites found and the percentage of administered dose are as follows: alkaline hydrolyzable conjugates, 0.48%; monoacetyl-3,3'-dimethoxybenzidine, 0.27%; free 3,3'-dimethoxybenzidine, 0.22%; and diacetyl-3,3'-dimethoxybenzidine, 0.22%. Much of the radioactivity from the dose (17.6%) was not extractable into benzene at alkaline pH. These water soluble metabolites were not characterized.

Lynn et al. (1980) studied the metabolism of Niagara Blue 4B in rats and dogs. Four male Sprague-Dawley rats were given a single dose (100 mg/kg) of Niagara Blue 4B in water by gavage. Urine was collected at 24-hour intervals and analyzed for 3,3'-dimethoxybenzidine by GC/MS. Two female mongrel dogs were given 100 mg/kg Niagara Blue 4B in food, and urine was

collected at 24-hour intervals for 3 days and analyzed for 3,3'-dimethoxybenzidine. The percentage of the administered dose excreted as 3,3'-dimethoxybenzidine after 72 hours was variable in the rats: 0.17%±0.18 (mean±SD of four rats). In addition to 3,3'-dimethoxybenzidine, monoacetyl-3,3'-dimethoxybenzidine was identified in the rat urine. In dogs, 0.03% (mean of two dogs) of the administered dose was excreted as 3,3'-dimethoxybenzidine 48 hours after dosing.

4.4. EXCRETION

Bowman et al. (1982) studied the excretion ^{14}C-Niagara Blue 4B in male Fischer 344 rats that received a single oral dose of 12 mg/kg ^{14}C-Niagara Blue 4B by gavage. Urine and feces were collected at intervals of 0-8, 8-16, 16-24, 24-48, 48-96, 96-144 and 144-192 hours after dosing. Peak excretion of ^{14}C in urine and feces occurred between 8 and 16 hours after dosing. At 144-192 hours after dosing, detectable levels of ^{14}C were still being excreted. Results showed that 74.4% of the administered dose was excreted in the feces, with 12% of the dose being excreted as intact dye in the feces. Radioactivity in the urine accounted for 18.8% of the administered dose.

4.5. SUMMARY

As indicated by excretion studies, at least 18% of an oral dose of Niagara Blue 4B was absorbed from the gastrointestinal tract of rats and was widely distributed throughout the body (Bowman et al., 1982). 3,3'-Dimethoxybenzidine has been identified in the urine of workers occupationally exposed to the dyes (Lowry et al., 1980; Genin, 1977) and in the urine of rats and dogs treated orally with Niagara Blue 4B (Bowman et al., 1982; Lynn et al., 1980). Alkaline hydrolyzable conjugates, monoacetyl-3,3'-dimethoxybenzidine and diacetyl-3,3'-dimethoxybenzidine were also found in the urine

of the rats (Bowman et al., 1982; Lynn et al., 1980). Peak excretion of radioactivity occurred 8-16 hours after oral exposure to Niagara Blue 4B in rats (Bowman et al., 1982). Approximately 75 and 19% was excreted in the feces and urine, respectively.

5. EFFECTS

5.1. CARCINOGENICITY

5.1.1. Animal Studies. Pertinent data regarding the carcinogenicity of Niagara Blue 4B in animals could not be located in the available literature as cited in the Appendix. NTP (1986) has performed a chronic drinking water study on 3,3-dimethoxybenzidine (a metabolite of Niagara Blue) using rats; histopathology is in progress. IARC (1982) concluded that evidence is sufficient to classify 3,3'-dimeth- oxybenzidine, a metabolite of Niagara Blue 4B, as an animal carcinogen.

5.1.2. Human Studies. Genin (1977) found benzidine in the urine of 8/22 workers and 3,3'-dimethoxybenzidine in the urine of 3/22 workers exposed to benzidine-based dyes. The urinary levels ranged from trace amounts to 0.3 µg/mL. Upon examination of company records of an unspecified number of workers, Genin (1977) found five cases of bladder tumors. Three of the bladder tumors occurred in workers who dried and ground direct azo dyes. These workers were exposed for 3-24 years and had latent periods of 18-43 years. The intensity of exposure to dyes was not measured.

5.2. MUTAGENICITY

The mutagenicity testing of Niagara Blue 4B is summarized in Table 5-1. Reid et al. (1984) and Prival et al. (1982 abstract; 1984) found that Niagara Blue 4B was mutagenic in frameshift-sensitive tester strains (TA1538, TA98) of Salmonella typhimurium using a preincubation protocol. Both of these investigators found that the mutagenicity of Niagara Blue 4B was greatly enhanced when hamster S9 mix plus the reducing agent flavin mononucleotide (FMN) or rat S9 mix plus rat fecal bacteria extract was included in the testing. This finding indicates that the reduction of the

TABLE 5-1

Mutagenicity Testing of Niagara Blue 4B

Assay	Indicator Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comments	Reference
Reverse mutation	Salmonella typhimurium TA1538	at least 7 impurities	20-minutes at 37°C preincubation step followed by plate incorporation	0.25-1.0 µmoles/plate	+S-9 rat +S-9 rat and rat cecal bacterial extract +S-9 hamster + FMN	+ + +	reduction by glutflora reducing system and FMN greatly enhanced mutagenic response; the compound was not tested in the absence of S-9	Reid et al., 1984
Reverse mutation	S. typhimurium TA98	commercial grade	30-minutes at 30°C preincubation step followed by plate incorporation	0.1-1.0 µmoles/plate	+S-9 hamster +S-9 and FMN	- +	FMN greatly increased mutagenic activity; not tested in the absence of S-9	Prival et al., 1982 Abstract, 1984
UDS	male F344 rat hepatocytes	NR	in vivo, gavage in vitro	NR	none	=	NC	Mirsalis et al., 1983 Abstract
L5178Y/TK+/- Gene mutation Assay	mouse lymphoma cells	NR	liquid suspension	NR	±S-9	±	more small colonies than large colonies were reported indicating both mutagenic and clastogenic activity	Rudd et al., 1983 Abstract

NR = Not reported; NC = no comment

azo bond to release free o-dianisidine appears to be one important step in activating Niagara Blue 4B to a mutagen.

Mirsalis et al. (1983) reported in an abstract that no increases in unscheduled DNA synthesis (UDS) were found in male F344 rat hepatocytes either in in vitro or in vivo tests. In another abstract, it was reported that Niagara Blue 4B produced an increased in trifluorothymidine resistant (TK^-) colonies in L5178Y mouse lymphona cells when S9 was present in the assay. The authors indicated that more small colonies were induced than larger colonies. This finding would indicate that Niagara 4B may be both mutagenic and clastogenic. It should be stressed that the studies of Mirsalis et al. (1983) and Rudd et al. (1983) are reported in abstract form, and thus cannot be critically reviewed.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenic effects after oral or inhalation exposure to Niagara Blue 4B could not be located in the available literature as cited in the Appendix.

A study by Beaudoin (1968) showed Niagara Blue 4B to be teratogenic in Wistar rats after intraperitoneal injection. Groups of 9-35 rats were injected intraperitoneally with a 2% aqueous dye solution on day 8 of gestation at doses of 70, 140 or 200 mg/kg. At the same time, 5 control rats were injected with distilled water and 15 controls were left untreated. Dams were killed on day 20, uteri were removed and the number of resorption sites and live fetuses were counted. Fetuses were fixed in Bouin's fluid or 95% alcohol for later examination. Results showed a dose-related increase in the number of resorptions. A dose-related increase in the number of malformed survivors was also observed. Anomalies found included anophthalmia, hydrocephalus, exencephaly, microphthalmia, vertebral defects,

encephalomeningocele, megalophthalmia and tailless fetuses. Exposure to the highest dose caused the deaths of 10/35 dams. Thirteen dams receiving unspecified doses of Niagara Blue 4B showed a decrease in weight gain, which was most significant during days 8-13.

In a study by Lloyd and Beck (1966), pregnant Wistar rats were injected subcutaneously on gestation day 8.5 with a 1% aqueous solution of Niagara Blue 4B (91% pure). Four groups of 11-13 dams each were injected with 50, 75, 100 or 150 mg/kg. No control group data were provided. Dams were killed on day 20.5, uteri were removed and the number of resorption sites and live fetuses were counted. Live fetuses were then examined for external malformations. A dose-related increase in the number of resorptions occurred, with 100% of 50 implantations being resorbed at the 150 mg/kg dose level. Malformations were found in 3/91 live fetuses in the lowest dose group. No other malformations were observed. Deaths of dams occurred at incidences of 1/12 at 75 mg/kg, 2/13 at 100 mg/kg and 6/11 at 150 mg/kg.

Lloyd and Beck (1966) also tested the hypothesis that the resorptions occurring before 20.5 days represented fetal toxicity rather than the nonviability of malformed fetuses. Groups of 8-13 dams were injected subcutaneously with 100 mg/kg of Niagara Blue 4B on day 8.5 of gestation and killed on day 11.5, 14.5 or 20.5. The percentages of resorptions were 47.8, 61.7 and 56.6% in dams killed on days 11.5, 14.5 and 20.5, respectively. The results indicate that most resorptions seen at term were due to deaths of fetuses within 3 days of treatment and that the deaths represented a direct toxic effect rather than a consequence of malformation.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the reproductive effects of Niagara Blue 4B could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Chronic oral or inhalation studies of Niagara Blue 4B were not available. In a subchronic study, groups of 20 male and 20 female rats of unspecified strain were administered 1000 mg/kg of commercial grade Niagara Blue 4B by gavage, 5 days/week for 30 days for a total of 22 doses (Leist, 1982). Controls were given an "appropriate" vehicle not containing the dye. Unspecified numbers of rats were killed following treatment and some were killed after a 2-week recovery period. The following indicators of toxicity were unaffected: clinical signs, mortality, food consumption, urinalysis, hematology and clinical chemistry. The skin and organs of the test rats turned blue. Upon histological examination of liver, kidneys, adrenals and spleen a reversible infiltration of blue color in the kidney tubules was noted. Reversible increased kidney weight and decreased weight of the adrenals was observed.

5.6. OTHER RELEVANT INFORMATION

Leist (1982) reported that the acute oral LD_{50} of Niagara Blue 4B in rats was >5000 mg/kg, a dose that produced no toxic effects.

5.7. SUMMARY

Pertinent data regarding the carcinogenicity of Niagara Blue 4B in animals could not be located in the available literature as cited in the Appendix. NTP (1986) has performed a chronic drinking water study of 3,3-dimethoxybenzidine using rats; histopathology is in progress. Dimethoxybenzidine is a metabolite of Niagara Blue and has been observed in the urine of exposed animals and humans. Bladder cancer has been reported in workers occupationally exposed to azo-dyes (Genin, 1977).

Niagara Blue 4B gave positive results in Salmonella typhimurium strains TA1538 and TA98 with rat or hamster S-9 activation, and mutagenic activity

was enhanced when FMN or bacterial reduction was included in the system (Reid et al., 1984; Prival et al., 1982, 1984). No increase in UDS was observed in rat hepatocytes either *in vivo* or *in vitro* (Mirsalis et al., 1983). Increased chromosomal aberrations were found in L51784 mouse lymphoma cells with metabolic activation (Rudd et al., 1983).

No data regarding teratogenic effects after oral or inhalation exposure to Niagara Blue 4B were available. Niagara Blue 4B caused a dose-related increase in resorption and malformed fetuses in rats following intraperitoneal injection (Beaudoin, 1968) and increased resorptions in rats following subcutaneous injection (Lloyd and Beck, 1966). Pertinent data regarding the reproductive effects of Niagara Blue 4B could not be located in the available literature as cited in the Appendix.

The chronic and subchronic toxicity of Niagara Blue 4B has not been adequately described. The only study found was a 30-day study in which the only effects observed in rats dosed with 1000 mg/kg/day, 5 days/week were blue coloration, increased kidney weight and decreased adrenal weight (Leist, 1982). These effects were not observed in rats after a 2-week recovery period.

6. AQUATIC TOXICITY

Pertinent data regarding the effects of Niagara Blue 4B on aquatic biota could not be located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

OSHA/NIOSH (1980) concluded that 3,3'-dimethoxybenzidine dyes may present a cancer risk to humans and recommended that they be handled with caution and that exposure be minimized. U.S. EPA (1981) did not require testing of 3,3'-dimethoxybenzidine-based dyes.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the effects of Niagara Blue 4B could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Pertinent data regarding the carcinogenicity of Niagara Blue 4B in animals could not be located in the available literature as cited in the Appendix. NTP (1986) has performed a chronic drinking water study of 3,3-dimethoxybenzidine using rats; histopathology is in progress. Dimethoxybenzidine is a metabolite of Niagara Blue and has been observed in the urine of exposed animals and humans. Bladder cancer has been reported in workers occupationally exposed to dyes (Genin, 1977).

The mutagenicity of Niagara Blue 4B in frameshift sensitive tester strains of Salmonella typhimurium was greatly enhanced when flavin mononucleotide (a reducing agent) or gut flora reduction was included in the testing (Reid et al., 1984; Prival et al., 1982, 1984). This finding indicates that reduction of the azo bond is one important step in activating Niagara Blue 4B to a mutagen. In an abstract, no increases in unscheduled DNA systhesis were reported in rat hepatocytes after in vivo or in vitro exposures to Niagara Blue 4B (Mirsalis et al., 1983). In another abstract increased mutant colonies were reported in L51784 mouse lymphoma cells with S9 metabolic activation (Rudd et al., 1983).

No data regarding teratogenic effects after oral or inhalation exposure to Niagara Blue 4B were available. Niagara Blue 4B caused a dose-related increase in resorptions and malformed fetuses in rats following intraperitoneal injection (Beaudoin, 1968) and increased resorptions in rats following subcutaneous injection (Lloyd and Beck, 1966). Pertinent data regarding the reproductive effects of Niagara Blue 4B could not be located in the available literature as cited in the Appendix.

The chronic and subchronic toxicity of Niagara Blue 4B has not been adequately described. The only study found was a 30-day study in which the only effects observed in rats dosed with 1000 mg/kg/day, 5 days/week for 30 days were blue coloration, increased kidney weight and decreased adrenal weight (Leist, 1982). These effects were not observed after a 2-week recovery period. This study is inadequate for RfD derivation.

Niagara Blue 4B is a 3,3'-dimethoxybenzidine-based dye. 3,3'-Dimethoxybenzidine has been identified in the urine of rats and dogs treated orally and in the urine of workers occupationally exposed to dyes (Bowman et al., 1982; Lynn et al., 1980; Lowry et al., 1980). From company records, Genin (1977) found several bladder cancer cases in workers occupationally exposed to dyes and identified 3,3'-dimethoxybenzidine in the urine of dye-exposed workers. Although workers were exposed to mixtures of benzidine- and 3,3'-dimethoxybenzidine-based dyes, the limited epidemiological evidence as well as the finding of 3,3'-dimethoxybenzidine, a known animal carcinogen (IARC, 1982), in the urine leads to the conclusion that Niagara Blue 4B may present a risk to man (OSHA/NIOSH, 1980). No carcinogenicity studies of Niagara Blue in animals were available at the time this report was written; however, an NTP (1986) chronic drinking water study of 3,3-dimethoxybenzidine using rats is in progress and reported by personal communication with the CAG to be positive at several tumor sites.

Taken together, the presence of a carcinogenic metabolite (3,3-dimethoxybenzidine) of Niagara Blue in test animals and exposed workers raises a serious concern about the human cancer potential. IARC considers dimethoxybenzidine to have sufficient animal evidence (IARC Group 2B), and that EPA would likely come to the same conclusion regarding 3,3-dimethoxybenzidine. NTP is reported to have a tumorigenic response with

drinking water exposure of rats to 3,3-dimethoxybenzidine. Based on these data, it is appropriate to provisionally give 3,3-dimethoxybenzidine an EPA Group B2 weight-of-evidence classification. By virtue of this metabolite being identified with exposure to Niagara Blue, it is similarly appropriate to place Niagara Blue in a provisional EPA Group B2 classification as well. A cancer potency derivation for Niagara Blue will have to await a further analysis of the dimethoxybenzidine data and/or the testing of Niagara Blue itself in a bioassay.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The only study available concerning the subchronic toxicity of Niagara Blue 4B was a 30-day study in which reversible increased kidney weight and decreased adrenal weight were observed in rats given a 1000 mg/kg/day dose of Niagara Blue 4B by gavage 5 days/week for 30 days. Since these effects were not observed in rats killed after a 2-week recovery period, they were reversible. The short duration of the study and the failure of the study to demonstrate definitive toxic effects precluded gathering of sufficient data to derive an RQ (Table 9-1).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Pertinent data describing the carcinogenicity of Niagara Blue 4B in animals were not available. NTP (1986) is testing a metabolite of Niagara Blue, 3,3-dimethoxybenzidine, in rats in a chronic drinking water study and histopathology is in progress. Genin (1977) found cases of bladder tumors in workers occupationally exposed to dyes and also detected 3,3'-dimethoxybenzidine in the urine of dye-exposed workers. Lowry et al. (1980) also detected 3,3'-dimethoxybenzidine in the urine of workers occupationally exposed to dyes. The limited epidemiological evidence and the finding of 3,3'-dimethoxybenzidine, a known animal carcinogen (IARC, 1982), in the urine of exposed workers leads to the conclusion that Niagara Blue 4B may present a risk to humans.

Taken together the presence of a carcinogenic metabolite (3,3-dimethoxybenzidine) of Niagara Blue in test animals and exposed workers raises a serious concern about the human cancer potential. IARC considers dimethoxybenzidine to have sufficient animal evidence (IARC Group 2B), and EPA would likely come to the same conclusion regarding 3,3-dimethoxybenzidine. NTP is reported to have a tumorigenic response with drinking

TABLE 9-1

Niagara Blue 4B

Minimum Dose (MED) and Reportable Quantity (RQ)

Route:	
Dose:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data are not sufficient for deriving an RQ.

water exposure of rats to 3,3-dimethoxybenzidine. Based on these data, it is appropriate to provisionally give 3,3-dimethoxybenzidine an EPA Group B2 weight-of-evidence classification. By virtue of the metabolite being identified with exposure to Niagara Blue, it is similarly appropriate to place Niagara Blue in a provisional EPA Group B2 classification as well. A cancer potency derivation for Niagara Blue will have to await a further analysis of the dimethoxybenzidine data and/or the testing of Niagara Blue itself in a bioassay.

10. REFERENCES

AATCC (American Association of Textile Chemists and Colorists). 1985. AATCC Buyers' Guide. Textile Chemist and Colorist. 17: 80.

Beaudoin, A.R. 1968. Teratogenic activity of six disazo dyes in the Wistar albino rat. Proc. Soc. Exp. Biol. Med. 127: 215-268.

Beaudoin A.R. and M.J. Pickering. 1960. Teratogenic activity of several synthetic compounds structurally related to Trypan Blue. Anat. Rec. 137: 297-305.

Bowman, M.C., W.L. Oller, C.R. Nony, K.L. Rowland, S.M. Billedeau and L.K. Lowry. 1982. Metabolism and distribution of 2 carbon-14-labeled benzidine-congener-based dyes in rats as determined by gas chromatography, high pressure liquid chromatography and radioassays. J. Anal. Toxicol. 6(4): 164-174.

Brown, D. and P. Laboureur. 1983. The degradation of dyestuffs: Part I. Primary biodegradation under anaerobic conditions. Chemosphere. 12: 397-404.

Brown, D., H.R. Hitz and L. Schaefer. 1981. The assessment of the possible inhibitory effect of dyestuffs on aerobic wastewater bacteria. Experience with a screening test. Chemosphere. 10(3): 245-261.

Genin, V.A. 1977. Formation of blastomogenic diphenylamino derivatives as a result of the metabolism of direct azo dyes. Vopr. Onkol. 23(9): 50-52. (Rus.) (Cited in NIOSH, 1980)

Haag, W.R. and T. Mill. 1985. Direct and indirect photolysis of azo dyes. Summary Report. EPA Contract 68-02-3968. Versar, Inc. Subcontract 867-1, Springfield, VA.

IARC (International Agency for Research on Cancer). 1982. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France. Supplement 4, p. 116-118.

Jones, T.C. 1979. Preliminary Risk Assessment Phase 1. Benzidine, Its Congeners and Their Derivative Dyes and Pigments. Office of Pesticides and Toxic Substances, U.S. EPA, Washington, DC. EPA-560/11-80-019.

Kuehni, R.C., J.C. King, R.E. Phillips, et al. 1979. Dyes, application and evaluation. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 8, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., New York. p. 302-305.

Leist, K.H. 1982. Subacute toxicity studies of selected organic colorants. Ecotoxicol. Environ. Saf. 6(5): 457-463.

Lloyd, J.B. and F. Beck. 1966. Relation of chemical structure to teratogenic activity among bisazo dyes. A re-evaluation. J. Embryol. Exp. Morphol. 16(1): 29-39.

Lowry, L.K., W.P. Tolos, M.F. Boeniger, C.R. Nony and M.C. Bowman. 1980. Chemical monitoring of urine from workers potentially exposed to benzidine-derived azo dyes. Toxicol. Lett. 7: 29-36.

Lynn, R.K., D.W. Danielson, A.M. Ilias, J.M. Kennish, K. Wong and H.B. Matthews. 1980. Metabolism of bisazobiphenyl dyes derived from benzidine, 3,3'-dimethylbenzidine or 3,3'-dimethoxybenzidine to carcinogenic aromatic amines in the dog and rat. Toxicol. Appl. Pharmacol. 56(2): 248-258.

Mirsalis, J., K. Tyson, J. Beck, et al. 1983. Induction of unscheduled DNA synthesis (UDS) in hepatocytes following in vitro and in vivo treatment. Environ. Mutagen. 5: 482.

NIOSH (National Institute for Occupational Safety and Health). 1984. Current Awareness File. Registry of Toxic Effects of Chemical Substance (RTECS). NIOSH, Cincinnati, OH.

NTP (National Toxicology Program). 1986. Management Status Report. Dated 3/12/86.

OSHA/NIOSH (Occupational Safety and Health Administration/National Institute for Occupational Safety and Health). 1980. Health Hazard Alert: Benzidine, O-Tolidine and O-Dianisidine-Based Dyes. DHHS(NIOSH) Publ. No. 81-106.

Porter, J.J. 1973. Stability of acid, basic and direct dyes to light and water. Text. Res. J. 43(12): 735-744.

Prival, M.J., V.D. Mitchell, M. Peiperl, V. Vaughan-Dellarco and S.J. Bell. 1982. Evaluation and application of a protocol for testing azo dyes for mutagenicity in Salmonella typhimurium. Environ. Mutagen. 4: 414.

Prival, M.J., S.J. Bell, V.C. Mitchell, M.D. Peiperl and V.L. Vaughan. 1984. Mutagenicity of benzidine and benzidine-congener dyes and selected monoazo dyes in a modified Salmonella assay. Mutat. Res. 136(1): 33-47.

Reid, T.M., K.C. Morton, C.Y. Wang and C.M. King. 1984. Mutagenicity of azo dyes following metabolism by different reductive/oxidative systems. Environ. Mutagen. 6: 705-717.

Rudd, C.J., A.D. Mitchell and J. Spalding. 1983. L5178Y mouse lymphoma cell mutagenesis assay of coded chemicals incorporating analyses of the colony size distributions. Environ. Mutagen. 5: 419.

Society of Dyers and Colourists. 1971a. Colour Index, Vol. 3, 3rd ed. Lund Humphries, Bradford, U.K. p. 4208.

Society of Dyers and Colourists. 1971b. Colour Index, Vol. 2, 3rd ed. Lund Humphries, Bradford, U.K. p. 2226.

Steadman, T.R., E.W. Helper, T. Parsons, G.E. Wilkins and N.P. Phillips. 1977. Industrial Process Profiles for Environmental Use: Chapter 7. Organic Dyes and Pigments Industry. EPA-600/2-77-023g. NTIS PB281479. p. 69.

Takemura, N., T. Akiyama and C. Nakahama. 1965. A survey of the pollution of the Sumida River, especially on the aromatic amines in the water. Inter. J. Air Pollut. 9(10): 665-670.

U.S. EPA. 1977. Computer print-out of non-confidential production data from TSCA inventory. OPTS, CID, U.S. EPA, Washington, DC.

U.S. EPA. 1981. Benzidine, O-Tolidine and O-Dianisidine-Based Dyes Response to the Interagency Testing Committee. Federal Register. 46(214): 55004-55006.

U.S. EPA. 1986a. Graphical Exposure Modeling System (GEMS). Octanol Water Partition Coefficient (CLOGP) data base. U.S. EPA, Washington, DC.

U.S. EPA. 1986b. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

USITC (U.S. International Trade Commission). 1981. Imports of Benzenoid Chemicals and Products 1980. USITC Publ. 1163, Washington, DC. p. 57.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982. USITC Publ. 1422, Washington, DC. p. 60.

USITC (U.S. International Trade Commission). 1984. Imports of Benzenoid Chemicals and Products 1983. USITC Publ. 1548, Washington, DC. p. 51.

USITC (U.S. International Trade Commission). 1985. Synthetic Organic Chemicals. U.S. Production and Sales, 1984. USITC Publ. 1745, Washington, DC. p. 66.

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

GLOBAL
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in April, 1986. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985-1986. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

Jaber, H.M., W.R. Mabey, S.T. Liu, T.W. Chow and H.L. Johnson. 1984. Data aquisition for environmental transport and fate screening for compounds of interest in the Office of Solid Waste. EPA 600/6-84-010. NTIS PB84-243906. SRI International, Menlo Park, CA.

NTP (National Toxicology Program). 1986. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1985. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.